(b) drying the substrate whereby the target polypeptide or the probe polypeptide directly adsorbs on the surface of the substrate.

68. (New) The method of claim 67, wherein the amount of the probe polypeptide or the target polypeptide contacted with the substrate in step (c) ranges from about 10^{-20} to about 10^{-14} moles.

69. (New) The method of claim 67, wherein the aliquot is from about 0.1nL to about 500 nL.

70. (New) The method of claim 67, wherein the drying is air-drying conducted for a period ranging from about 5 minutes to about 60 minutes.

REMARKS:

Claim 29 is amended; the marked up version of the amended claim is attached hereto pursuant to 37 C.F.R. § 1.121(c)(ii). New claims 55-70 are added. New claims incorporate the limitations of originally filed claims 1-54 and, thus, do not introduce new matter. Claims 29-42 and 55-70 are pending in the application. Reexamination and reconsideration of the application, as amended, are respectfully requested.

Claims 29-42 are rejected under 35 U.S.C. § 102(e) as being anticipated by Head et al. (U.S. Patent No. 6,322,968 B1; the '968 patent). This rejection is respectfully traversed.

The Examiner appears to believe that the '968 patent anticipates instant claim 29 because it teaches that a nucleic acid sequencing reagent may be non-specifically attached to a charged surface, such as an amino-modified solid surface. The Examiner also indicates that the '968 patent anticipates instant claim 29 because the '968 patent teaches that the sequencing reagent can be specifically attached to a solid surface by means of a non-covalent bond, for example, a biotin-labeled oligonucleotide may be immobilized to an avidin- or strepavidin-coated substrate. Applicants disagree.

Claim 29, as amended, emphasizes that in the present invention, biopolymers are directly adsorbed on the substrate by contacting a biopolymer with a surface of the substrate and drying the substrate. It is an unexpected discovery of the present invention that modified substrates, such as plasma-aminated polypropylene and polysterene substrates, are capable of direct and stable adsorption of biomolecules without any chemical spacer arms or links by drying biopolymer solutions on the substrates (page 8, lines 13-21). Of course, a biomolecule directly adsorbed on the surface itself may serve as a linker for attachment of another biomolecule.

Because in the present invention biopolymers are dried on the substrates, substantially all biopolymers present in the biopolymer solution precipitate on and become adsorbed by the substrate (any loosely bound biomolecules are subsequently removed by a simple rinsing). Accordingly, in this method, small volumes of very diluted biopolymer solutions may be used to form assay articles.

In this respect, applicants respectfully draw the Examiner's attention to Examples 1 and 2 on pages 16-18 of the present invention. In Example 1, 10 nl aliquots of 1nM cDNA solutions prepared in sodium bicarbonate buffer (pH 9) are applied to an aminated polypropylene substrate. Following the application of the cDNA, the substrates are air-dried at 35°C for 15 minutes. In Example 2, 0.5 µL spots of diluted Human IgG in sodium bicarbonate (50 mM, pH 9) and 4% sodium sulfate are pipetted onto an amino polypropylene strip. The strip is air-dried for 60 min. at 25°C.

Consequently, the present invention provides a number of advantages over the conventional methods. The advantages include, for example, a simplification of the production of biopolymer arrays and a decrease in their manufacturing costs (page 5, lines 25-30).

The statement of the '968 patent that a nucleic acid sequencing reagent may be non-specifically attached to a charged surface (column 8, lines 63-65) does not anticipate present claim 29 because it is not enabled by the disclosure. The '968 patent does not provide any general guidance, much less specific examples, on how such a non-specific attachment may be carried out.

Moreover, as explained in the Introduction of the present specification, it is generally understood in the art that the immobilization of biopolymers on substrates require either direct covalent interaction between modified substrates and biopolymers or covalent bonding via spacers or linkers.

Furthermore, although it is generally known that some biomolecules may be immobilized on substrates by adsorption, it is also known that the drying process may lead to denaturation of the biomolecule. Typically, the degree of denaturation is dependent upon the drying conditions and also upon the stability of the biomolecule. Accordingly, it is highly unlikely that one skilled in the art would have purposely dried down a biomolecule on a substrate for immobilization purposes. In addition, although it is well known that the length, sequence and structure of a nucleic acid generally influence adsorption onto solid supports, the mechanism is poorly understood. Thus, it remains to be a pure speculation as to whether or not a particular biomolecule can be adsorbed onto a particular surface by drying without denaturation or loss in function or dissociation from the surface upon wetting.

Therefore, absent further guidance, the statement quoted by the Examiner is only a speculation that does not enable a worker of ordinary skill to arrive at instant claim 29.

Additionally, the statement quoted by the Examiner has no teaching whatsoever of adsorption by drying as required by instant claim 29. Therefore, the statement of the '968 patent that a nucleic acid sequencing reagent may be non-specifically attached to a charged surface quoted by the Examiner does not anticipate instant claim 29.

The description of a specific attachment of the sequencing reagent to a solid surface by means of a non-covalent bond referenced by the Examiner also does not anticipate present claim 29 because it does not teach a direct adsorption as defined by the instant specification. The instant specification defines the term "direct adsorption" as an adsorption without any chemical linkers. It is further noted in the specification that "unlike the related art, which uses chemical cross-linking of biopolymers to the substrates, the present invention allows immobilization of both

unmodified and modified biopolymers on substrates by simple air-drying on the substrate" (page 8, lines 13-21). Finally, the specification provides a possible theoretical explanation of the term "direct adsorption" as a result of ionic and hydrophobic interaction between biopolymers and their substrates (page 8, lines 22-28).

The specific attachment method cited by the Examiner requires labeling of a biomolecule with biotin and coating the substrate with avidin (or strepavidin) in order to form a non-covalent bond between biotin and avidin (or strepavidin) and to attach the biomolecule to the substrate (column 9, lines 3-7). Such bonding between biotin and avidin is known to be very strong (association constant of 10^{15} M^{-1} (see attached web article) and involves chemical interaction rather than "direct adsorption" as required by claim 29.

Although the present invention teaches that a biopolymer may be indirectly labeled by biotin, the purpose of such labeling is entirely different from that of the '968 patent. As explained on page 13, line 31-page 14, line 4, in the present invention, the biotin moiety may be attached to a biomolecule to facilitate a detection of a probe-target complex. Accordingly, the biotin moiety must be available for interaction with stretavidin-alkaline phosphatase conjugate. Therefore, unlike in the '968 patent, in the present invention, the biotin moiety does not participate in the immobilization of a biomolecule on a substrate; instead, a biomolecule is immobilized on a substrate by adsorption.

In summary, the description of a specific attachment of the sequencing reagent to a solid surface by means of a non-covalent bond recited in the '968 patent does not teach adsorption of biomolecules on a substrate by drying. Accordingly, the statement cited by the Examiner does not anticipate instant claim 29.

The '968 patent does not suggest instant claim 29, because it does not suggest adsorbing biomolecules by drying. At most, the '968 patent teaches a non-specific adsorption of a nucleic acid sequencing reagent on a solid substrate by incubating the solid substrate with the agent overnight in a presence of a cationic agent (column 8, lines 60-63, and Example 3 in column 18).

Because the incubation method of the '968 patent does not involve drying of a biopolymer solution on the substrate, the efficiency of biopolymer adsorption depend on the rate of biopolymer diffusion through the solution toward the substrate and requires presence of the cationic agent. Accordingly, at the end of incubation, some biopolymers become adsorbed on the substrate, while others remain in the biopolymer solution, which is later removed (column 18, lines 37-42). As a result, the incubation method of the '968 patent requires considerably larger volumes and higher concentrations of biopolymer solutions, as compared to the drying method of the present invention, to achieve similar immobilization efficiencies.

For instance, Example 3 of the '968 patent involves placing 50 μl of 200 nM biopolymer solution in each well of the substrate. This is 5,000 times larger volume and 200 times higher concentration than those disclosed in the instant Example 1. Because the '968 patent uses such relatively larger volumes of biopolymer solutions, its primer solution does not dry in the wells after an overnight incubation (column 18, lines 38-42). By contrast, in the instant Example 1, the biopolymer solution dries after 15 minutes (page 16, lines 15-20).

Therefore, the '968 patent has no teaching or suggestion that would have motivated one skilled in the art to arrive at the method of present claim 29. Consequently, the '968 reference does not teach or suggest present claim 29. Claims 30-42 depend on claim 29, directly or indirectly, and are patentable over the '968 patent for at least the same reasons.

Applicants have added new claims 55-70 to further define alternative embodiments of the invention. Claims 55-63 depend on the patentable claim 29 and, thus, are patentable for at least the same reasons.

New claim 64 is patentable over the '968 patent. Independent claim 64 contains a limitation of "contacting either the probe or target polypeptide with a surface of the substrate under a condition sufficient for a direct adsorption of either the probe or target polypeptide on the substrate surface." The '968 patent has no teaching whatsoever of the immobilization of polypeptides on substrates, let alone the immobilization of polypeptides by direct adsorption on substrates. Therefore,

the '968 patent neither anticipates nor makes new claim 64 obvious. Claims 65-70 depend, directly or indirectly, on claim 64 and, therefore, are patentable for at least the same reasons.

In view of the foregoing, it is respectfully submitted that the application is in condition for allowance. Reexamination and reconsideration of the application, as amended, are requested.

If for any reason the Examiner finds the application other than in condition for allowance, the Examiner is requested to call the undersigned attorney at the Los Angeles, California telephone number 213-337-6700 to discuss the steps necessary for placing the application in condition for allowance.

Respectfully submitted,

HOGAN & HARTSON L.L.P.

Date: March 12, 2002

By:_____

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Version with markings to show changes made:

IN THE CLAIMS

Please replace the text of claim 29 with the following text:

29. (Amended) A method of detecting a target biopolymer contained in a sample, comprising the steps of:

(a) providing a modified substrate;

(b) providing a probe biopolymer that can form a complex with the target biopolymer;

(c) contacting either the probe or target biopolymer with a surface of the substrate [under a condition sufficient for a direct adsorption of] and drying the substrate whereby either the probe or target biopolymer directly adsorbs on the substrate surface to form a probe assay article or a target assay article, respectively;

(d) contacting the probe assay article with the target biopolymer, or contacting the target assay article with the probe biopolymer under a condition that allows the formation of a complex comprising the probe and the target biopolymers; and

(e) detecting and determining the presence of the complex as a measurement for the presence or the amount of the target biopolymer contained in the sample.